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# Disease-a-Month

# *Treatment of Tuberculosis*

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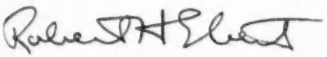

received his degree of Doctor of Philosophy in experimental pathology from Oxford University and his M.D. degree from the University of Chicago School of Medicine. He had an internship and assistant residency at Boston City Hospital. Dr. Ebert is Professor of Medicine at the University of Chicago and Head of the Division of Pulmonary Diseases. He is Chairman of the Committee for Medical Research of the National Tuberculosis Association, and has carried out laboratory investigations on the pathology of tuberculosis and the mode of action of antimicrobial agents.

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TREMENDOUS advances have been made in the treatment of tuberculosis during the past decade, and the results have been gratifying in terms of decreased morbidity and mortality. But the very success of therapy has led to some indifference on the part of many physicians toward the treatment of tuberculosis. It is assumed that tuberculosis is no longer a problem, and that the introduction of potent antimicrobial agents has so simplified therapy that tuberculosis may be treated in the office with a minimum of knowledge or understanding of the disease. The reverse is true. Since specific therapy does exist it is all the more important to have some understanding of the rationale for treatment, and its relationship to the special pathology and bacteriology of the disease. The problem cases today too often are those which were mismanaged at the time of initial treatment.

This review will deal mainly with pulmonary tuberculosis, for it is the commonest form of the disease and has been the subject of the most careful clinical studies. The major principles of treatment, however, are just as applicable to tuberculosis of other organs as to tuberculosis of the lung. At the end of the article the particular problems which relate to tuberculosis of other organs will be discussed briefly.

## BASIC CONCEPTS

To understand the treatment of tuberculosis it is necessary to have some basic knowledge of the pathology and bacteriol-

ogy of the disease as well as an understanding of host resistance to infection.

## Pathology

**The tubercle.**—The type of lesion which develops in response to infection with the tubercle bacillus depends on a variety of factors, including route of inoculation, the organ infected, the number and virulence of the infecting organisms and resistance of the host. But for the moment let us consider only the development of the basic lesion, first, in the animal which has had no previous contact with the bacillus and, second, in the animal which has had an infection.

Much can be learned from animal experimentation about the pathogenesis of the tubercle. The initial reaction to infection of the tuberculin-negative animal which has had no previous exposure to the tubercle bacillus is relatively mild. Polymorphonuclear leukocytes migrate from vessels in the infected area within the first 24–48 hours. The bacilli may be ingested by the polymorphonuclear leukocytes but survive within the cells and are released as the polymorphonuclear cells die. After 48 hours the exudate becomes predominantly mononuclear as monocytes migrate from surrounding vessels, and fixed tissue histiocytes are mobilized. It should be emphasized that this reaction is a sluggish one, for the tubercle bacillus on first contact with the host does not stimulate a very marked inflammatory response. Tubercle bacilli are ingested by mononuclear cells, but many bacilli can survive and even multiply within the cell. It is probably these mononuclear cells which are transformed into the typical epithelioid and giant cells which characterize the tubercle histologically, and it is believed that this transformation is stimulated by the lipids of the tubercle bacillus. During this early period of infection, i.e., the first one to two weeks, there is relatively little inhibition of multiplication of bacilli. The bacilli exist in a favorable environment for growth; oxygen is abundant, and despite phagocytosis by mononuclear cell, the bacilli continue to multiply intracellularly. Since the inflammatory response is minimal, there is little tendency for localization of infection, and bacilli may spread by direct expansion or via lymphatics to regional lymph nodes. There is good evidence that, in first infection, bacilli always spread to the regional nodes and that this is very rapid. Significant numbers of bacilli may be present in

regional nodes within an hour after inoculation. Many bacilli which find their way to lymph nodes are probably carried within mononuclear cells which migrate into lymphatics. The lymph node is a good filter for foreign bodies, including the tubercle bacillus, but does not always hold back every bacillus, so that some may gain access to the blood stream via the thoracic duct.

It has been possible to watch the development of a tubercle in living tissue from the time of inoculation (1), using a special technique developed by the Clarks (2). Their rabbit ear chamber provides a thin layer of living vascularized tissue which can be observed under high powers of magnification for weeks and months after inoculation with living virulent tubercle bacilli. This method is particularly suited to observations of the vascular response to infection.

During the first few weeks after inoculation the cells accumulate as described above, and the intensity of the response depends upon the numbers of organisms which are inoculated. During this initial phase of tissue reaction the vascular changes are relatively mild. There is mild dilatation of small blood vessels, and a few leukocytes adhere to vascular endothelium (evidence of mild endothelial damage), but these changes tend to be localized to areas where bacilli are lodged. Sometime between the 10th and 20th day after inoculation a much more intense inflammatory reaction occurs. This usually begins quite suddenly and is characterized by more generalized dilatation of small blood vessels, generalized sticking of leukocytes to vascular endothelium and a much greater migration of leukocytes into the tissues.

There is now a much more dramatic response to the tubercle bacilli, which, when first introduced, seemed to stimulate a very mild inflammatory reaction. Small vessels adjacent to areas where mononuclear cells have accumulated are widely dilated, and blood flow becomes sluggish and erratic. Stasis develops in many of these vessels, and this may progress to thrombosis and infarction of the tissue in which the tubercle bacilli are lodged. As the areas of necrosis coalesce a tubercle is formed with a central caseous area surrounded by inflammatory cells and dilated blood vessels.

What change has occurred to produce this more intense inflammatory reaction? Obviously there has been no fundamental change in the infecting organism, so that the change is asso-

ciated with an alteration in the way the host tissues respond to the bacillus. If we now test the animal with tuberculin it is found that an area of redness and induration develops in 24-48 hours, whereas the animal had previously been tuberculin negative. In other words, this heightened response and the development of necrosis are a manifestation of tuberculin allergy or hypersensitivity. Hypersensitivity to tuberculoprotein is a concept vital to the understanding of the problems of therapy, for this altered reactivity of the tissues of the host is responsible for the necrotic tubercle. And necrosis and caseation present the major barrier to the eradication of tuberculous infection.

The discussion of pathogenesis thus far has considered the development of a tubercle in the tuberculin-negative animal. What happens when tubercle bacilli are inoculated into an animal which has had prior infection and is tuberculin positive? An intense inflammatory reaction begins immediately, and extensive exudation occurs in the first 48 hours after inoculation. If the inoculum is large enough, necrosis develops within 48 hours. Something else has happened to the animal, however, besides the development of hypersensitivity at the time of first infection, so that re-infection is characterized by localization of the invading organisms and greater inhibition of multiplication. Thus tubercle bacilli are not carried to regional nodes, in ordinary circumstances, but tend to remain localized at the site of inoculation, and multiplication within cells is inhibited. This is a manifestation of active immunity. Immunity and allergy develop at the same time but are not identical and do not necessarily parallel each other. These phenomena will be discussed at more length when host resistance is considered.

In summary, the differences between primary and re-infection tuberculosis are as follows: (1) In primary infection the initial inflammatory response is minimal. During this period bacilli may be carried to other parts of the body and are always found in regional nodes. (2) With the development of tuberculin hypersensitivity there is a much more striking inflammatory response and necrosis and caseation develop. There is also the tendency to localize infection and inhibit the intra- and extracellular multiplication of bacilli. (3) Re-infection tuberculosis occurs in an animal which has already acquired

allergy and immunity, and the initial inflammatory reaction is marked and necrosis may develop within the first 48 hours. There is active inhibition of multiplication of bacilli and the invading organisms tend to be localized to the site of inoculation.

TYPES OF INFLAMMATORY REACTION.—Clinically it is useful to speak of different types of inflammatory reaction which occur in tuberculosis since the type of tissue reaction will determine to some extent the response to therapy. It is well to remember that these are rather arbitrary divisions and often are descriptive of the age of the process rather than of any fundamental difference in the tissue response. For example, certain lesions, particularly in the lung, are described as exudative because histologically they consist of a dense exudate of principally mononuclear cells. Obviously such lesions must be relatively recent and are most often seen in spread of disease from one part of the lung to another. Whether or not necrosis develops depends upon the number of bacilli and the inhibition of their growth together with the degree of hypersensitivity of the host. Such areas of pneumonic exudate may resolve completely. This does not mean that exudate is not an integral part of all fresh tubercles, but the more familiar tubercle goes on to central necrosis, as described earlier. This central caseous area is surrounded by epithelioid and giant cells together with small round cells thought to be lymphocytes. Since there is a natural tendency toward healing, fibrous tissue is laid down around the tubercle, its amount and density depending upon the age of the tubercle.

It is well to remember that the histologic picture of the tubercle as seen in fixed and stained preparations is only one moment in the history of this lesion and that even chronic infection is a dynamic, ever-changing process. Change is usually slow, and healing in particular is slow, but extension of the tuberculous process may be very rapid indeed.

There is one other pathologic phenomenon which has a most important bearing on the treatment of tuberculosis. Ordinarily the caseous center of a tubercle is semisolid, as the name implies. In certain poorly defined circumstances, this caseous material may become much more fluid, and if there is communication to the outside, as via a bronchus in the lung, the contents will drain and a cavity will form. Such cavities may

persist for years and are the usual source of a persistently positive sputum.

THE TUBERCLE BACILLUS.—It is customary in discussion of the pathology of tuberculosis to talk first about the bacillus and then the pathogenesis of tuberculosis. This was not done here because certain of the reactions of the host modify the bacillus in ways which have important implications in terms of treatment.

Mycobacterium tuberculosis is an acid-fast rod which is aerobic and grows slowly in a variety of media. Virulence is associated with the growth of bacilli in microscopic serpentine cords in culture, and if this ability is lost the organisms lose their virulence. The concept of virulence is an important one; and Rich (3) has defined it as "the relative ability of a given strain to survive and to reproduce progressively in the tissues of normal individuals of an animal species that is natively susceptible to the type from which the strain in question was derived." In other words, an avirulent strain such as BCG can produce the characteristic lesion of tuberculosis in the human host, but it lacks the ability to survive and reproduce progressively and thus cannot induce the disease tuberculosis. The qualities of the bacillus which confer virulence are obscure, but the effects of virulence are not. The virulent tubercle bacillus can survive in tissue fluid and within mononuclear cells and is killed by the host's defense with great difficulty.

Tubercle bacilli within the caseous material of the tubercle are not necessarily killed, but because of oxygen lack and the inhibiting effect of certain products of the necrotic area they do not multiply, and they survive in a much different metabolic state than actively multiplying bacilli. They may remain dormant for months and even years and still be capable of rapid multiplication when placed in a suitable environment. The altered metabolic state of bacilli within caseous areas is discussed further with principles of chemotherapy. Tubercle bacilli which persist within cavities are well supplied with oxygen and may multiply freely, in contrast to those lodged within caseous material.

In summary, the tubercle bacillus multiplies slowly, requires oxygen for multiplication, is not easily killed by the defense of the host and can survive in an altered metabolic state within the caseous lesion.

## Resistance to Infection

The ability of the host to contain the invading bacillus and prevent extension of the disease is a measure of the resistance of the host, both natural and acquired (4). That resistance is variable is a daily clinical observation.

Natural resistance.—Each species has a certain degree of natural resistance to tuberculous infection apart from immunity, and fortunately man has a relatively high degree of resistance. The guinea pig, in contrast, has little resistance, for infection is never completely controlled in this animal and ultimately is always fatal. Lurie (4) has been able to breed strains of rabbits which have a high degree of resistance to infection and other strains which have a low degree of resistance, so that within a given species there is considerable genetic variability in the reaction to infection. Such pure-bred strains cannot be found in human populations, but there is little doubt that by natural selection populations which have had long contact with the tubercle bacillus have acquired a considerable degree of natural resistance.

Lurie has observed a number of differences between susceptible and resistant strains of rabbits. The resistant race can suppress multiplication of bacilli both inside and outside of mononuclear cells, it shows a more rapid inflammatory response to infection, and the disease shows a diminished tendency to spread beyond the regional lymph nodes in primary infection. Not only is there greater initial resistance to infection, but acquired resistance seems to be enhanced in the resistant race over that in the susceptible race. There is evidence that adrenals of genetically susceptible rabbits secrete about twice as much hydrocortisone as do genetically resistant animals, whereas the resistant animals secrete larger amounts of corticosterone (5). Since hydrocortisone diminishes the inflammatory response to infection and also inhibits antibody production, this may be the major mechanism for genetic difference in susceptibility.

In addition to species difference in resistance, there is a difference too in the ability of various tissues to withstand infection. Muscle is rarely infected, and gut is much more resistant than lung. Lung, kidney and bone are commonly infected in the human host.

Acquired resistance.—Although hypersensitivity is so dra-

matic that it tends to obscure the development of immunity to the tubercle bacillus, an increased ability of the host to inhibit growth of tubercle bacilli and localize infection develops about the same time as tuberculin allergy. This is almost impossible to quantitate accurately because it is very difficult to measure circulating antibodies, and enhanced resistance seems to reside largely in the ability of mononuclear cells to inhibit intracellular growth of the tubercle bacilli and prevent spread. Such resistance cannot be passively transferred with serum and is conferred only by inoculation of the whole bacillus, living or dead. Although it is common to assume that a patient has some acquired resistance to infection if he reacts to tuberculin, it should be remembered that this is a measure of tuberculin allergy, and the fact that immunity exists is only inferred.

## Equilibrium between Host and Parasite

It is obvious that the outcome of tuberculous infection is determined by the balance between the number and virulence of the invading organisms and the resistance of the host. Even the original invasion is determined by this balance, for tissues vary in susceptibility. The portal of entry for bovine tuberculosis is the gut, since infected milk is the source of tubercle bacilli, and the intestinal mucosa is relatively resistant to infection. In contrast, the lung is much more susceptible, and this is the common portal of entry for human strains of tubercle bacilli. Bovine tuberculosis has been eliminated as a significant source of infection in the United States.

The spread of infection depends upon the balance between the number and virulence of the invading organisms and the resistance of the host. It is usually assumed that the virulence of tubercle bacilli producing clinical disease is relatively constant (at least there are almost no data on variations in virulence), but, of course, the number of infecting organisms is variable. Spread may occur in a number of ways. There is local spread of bacilli in tissue fluids to adjacent areas; and spread via lymphatics to regional nodes occurs in primary infection. Hematogenous spread may occur early in primary infection, or late in infection by the invasion of a blood vessel by a tuberculous lesion with spilling of organisms into the vessel. Tuberculosis of bone, of kidney and of meninges are examples of hematogenous disease, and miliary tuberculosis is

the classic example of acute hematogenous extension. Tuberculous cavities in the lung are the commonest source of direct extension of tuberculous disease. This is a form of intracanalicular spread, and the disease may extend to the bronchus, to other parts of the lung (bronchogenic spread), to the larynx, or bacilli may be swallowed in sufficient numbers to produce tuberculous enteritis.

In untreated tuberculosis there is often a rather delicate balance between the host and the parasite. Take, for example, the patient with a chronic tuberculous cavity which is present for months or even years and remains relatively unaltered. Bacilli multiply in the cavity wall and are constantly being drained via the bronchus; yet a bronchogenic dissemination does not occur and there is no other evidence of spread. Then very suddenly there may be infection of the opposite lung by bacilli aspirated from the cavity. Something must have happened to this balance between parasite and host which temporarily has thrown the balance in favor of the bacillus. Tuberculous infection often seems to be a see-saw in which the host is on the ascendency for a time, then the parasite.

It is obvious that the physician can affect the outcome of infection in two ways. He can attempt to alter the resistance of the host in a favorable manner, or he can try to control the number of infecting organisms. This is the basis of all treatment of tuberculosis, and if this is understood an approach to rational treatment can be made.

## THERAPY AIMED AT ALTERING HOST RESISTANCE

Until a little over a decade ago the keystone of therapy was the attempt to influence favorably the resistance of the host, and the most important aspects of this were good nutrition and bed rest.

NUTRITION.—There is good evidence that malnutrition has an unfavorable effect upon host resistance to tuberculous infection. Malnutrition, and particularly protein depletion which follows in the wake of war, seems to set the stage for reactivation of old disease. It therefore appears reasonable that the tuberculous patient should have a good diet and certainly one adequate in protein. There is little evidence to suggest, however, that anything more than an adequate diet is necessary. The use of vitamin supplements is customary but probably

does little good. Certainly an adequate state of nutrition is essential, and weight which has been lost should be regained. It must also be remembered that in the more acute phase of tuberculous infection the dietary requirements may be increased as a result of the increased metabolism associated with fever and tissue destruction.

BED REST AND SANATORIUM CARE.—Hospital or sanatorium care of the tuberculous patient has a twofold purpose. First, it isolates the patient from others in his immediate environment, particularly his family. Second, it is an attempt by the physician to affect favorably the patient's resistance. Few would argue with the first purpose, but since the introduction of potent antimicrobial agents some physicians take issue with the second. Before considering the arguments against bed rest in the sanatorium, let us examine what the physician attempts to accomplish, under ideal conditions, by providing rest for the tuberculous patient.

Consider the patient who has been told that he has active tuberculosis and will require a long period of treatment before he can return to normal life. Often this is a devastating blow, which is not necessarily eased by minimizing the danger of tuberculosis and the need for intensive therapy. The average patient's knowledge of tuberculosis is incomplete and inaccurate and often is based on half-remembered stories of family or friends who have been crippled by or died of tuberculosis. Once he recovers from the initial shock of the diagnosis he worries about his job, his family and all of his commitments. Has he infected his family, how will they get on without him, will he ever be able to work again?

The ideal of sanatorium care is to provide the setting for physical and emotional rest and the social services to relieve the anxieties associated with both the real and the imaginary problems arising from the illness. Social agencies can be mobilized to see that the family is cared for, careful examination of members of the family and other contacts can be done, and plans can be discussed for ultimate return to work. Above all, the patient can be educated to understand the nature of his disease, its real dangers and the imagined ones, and how it can be cured. He can look around him and see that there are others with the same affliction, many worse off than he and many who are well on the road to recovery. The removal of the patient from his home environment may seem to create difficulties, yet it relieves more

than it makes, for it provides a release from the day by day pressure of problems in the domestic environment. The patient is put to bed and cared for in an environment where this is the rule, and he need not feel guilty about it as he would at home. In a word, the patient is allowed to regress; all his needs are cared for and he does not need to solve any problems.

There is little doubt that this kind of regression and shielding from physical and emotional stress has a favorable effect upon the host in terms of combating tuberculous infection. In the days before chemotherapy it was common experience to see disease regress on bed rest in the sanatorium and progress again when the patient returned to active life. There is also little doubt that

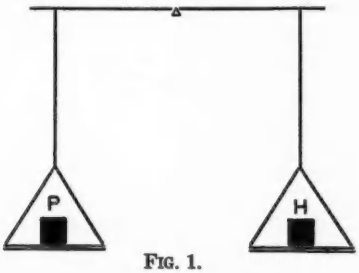


FIG. 1.

this kind of intensive rest therapy, which might continue for many months and even years, created serious problems of rehabilitation. The protected environment of the sanatorium often became more desirable than the outside world.

Unfortunately it is much more difficult to evaluate the role of bed rest and sanatorium care, now that potent drugs are available which attack the parasite. The problem can be illustrated by a series of diagrams: Suppose that the balance between parasite and host is as represented graphically in Figure 1, with the left side representing the number and virulence of the infecting organisms *(P)* and the right side host resistance *(H)*. The patient enters the sanatorium with evidence of extension of his disease. In other words, the parasite has tipped the balance toward progression of infection (Fig. 2). Sanatorium care increases host resistance sufficiently to reverse the balance in favor of healing, without directly affecting the number or virulence of the invading organism (Fig. 3). The introduction of antimicro-

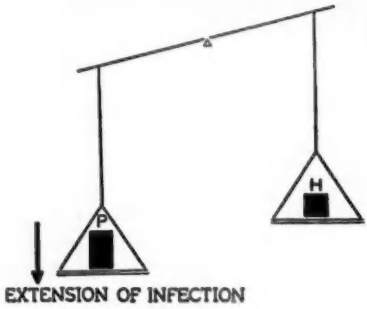


FIG. 2.

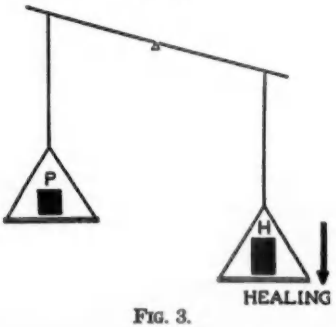


FIG. 3.

bial agents makes it much more difficult to evaluate the effect on host resistance. Suppose we start with Figure 2 again and only do something which affects the parasite. Host resistance remains the same, but the number of tubercle bacilli diminishes and the balance tips in favor of healing (Fig. 4). Now suppose we add an increase in host resistance to the picture by initiating bed rest (Fig. 5). It is difficult to measure and difficult to evaluate its importance, for the balance is already tipped in favor of healing by reducing the number of bacilli. Is it also necessary to tip the balance further by attempting to increase host resistance? Some say it is not necessary and advocate ambulatory care of active tuberculosis. Others believe that sanatorium care is as necessary as it was before the days of antimicrobial therapy.

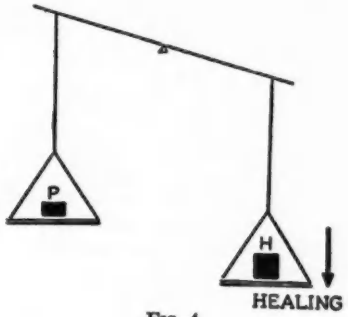


FIG. 4.

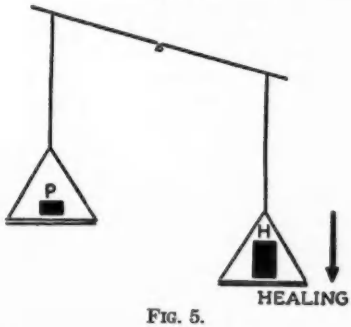


FIG. 5.

The answer probably lies between these extremes of opinion.

Certainly tuberculosis which is active and appears to be recent in origin is best treated in a hospital or sanatorium during the initial period of therapy. Complete bed rest is desirable if there is fever or other evidence of generalized toxicity from the infection. As signs and symptoms of active infection subside and there is other evidence of favorable progress in terms of x-ray improvement, decrease in amounts of sputum and the number of tubercle bacilli produced, the amount of bed rest can be modified. There is much to be said for mobilizing the patient as rapidly as is consistent with favorable progress. The endpoints of treatment are discussed a little later, but it can be stated here that therapy does not end in the hospital or sana-

torium and that rehabilitation is made much simpler by reducing the length of stay in bed and in the hospital. Many patients have been cured in a sanatorium, but many have been crippled psychologically in the pursuit of cure.

Obviously no absolute rules can be made for bed rest or sanatorium care. This must be individualized to suit the patient's needs. The patient with old fibrotic disease with low grade activity will benefit little from bed rest, whereas the patient with a fresh pneumonic infiltrate will benefit enormously.

In summary, bed rest and care in the hospital or sanatorium is calculated to affect the host resistance favorably. This is a less important facet of therapy than it was before the introduction of antimicrobial agents but still occupies an important place in treatment of active disease. Part of the effect of institutional care is psychologic, for it removes the patient from the emotional stress of his environment. Physical and emotional rest is desirable if not too prolonged. When used wisely it promotes healing. When used unwisely and for too long it makes it difficult for the patient to resume his duties in the world outside the sanatorium. Great reduction in the length of time the patient needs to spend in bed and in the sanatorium has made possible his more rapid rehabilitation.

HORMONE THERAPY.—Corticotropin and cortisone have a profound effect on all inflammatory processes, including tuberculous inflammation. While these hormones have been shown repeatedly to have a deleterious effect on a variety of infections, there is good evidence that they may be beneficial when given during the acute phase of infection together with adequate chemotherapy (6). Under ordinary conditions the inflammatory response to infection is one of the most important defense mechanisms of the host, but there are times when the inflammatory reaction may be so profound that the toxemia which it produces has an adverse effect on the host. An example of this is tuberculous meningitis. If the inflammation of the meninges becomes too extensive there is danger of basal block, and for this reason corticotropin and cortisone have been used together with antimicrobial agents by some clinicians in the treatment of meningitis during the early phase of the illness (7).

Such therapy is a deliberate attempt to manipulate the host response to infection by reducing the inflammatory reaction to infection. This may have a beneficial effect, but the purpose of

hormone therapy should be kept in mind and the inherent dangers of such treatment should be remembered.

## THERAPEUTIC MEASURES WHICH REDUCE THE NUMBER OF INFECTING ORGANISMS

### Chemotherapy

The concept of altering host resistance by bed rest, sanatorium care and the like is rather vague since we know so little about mechanisms. But the use of antimicrobial agents to tip the balance in favor of healing is a much more direct and understandable approach to therapy.

For years it was believed that chemotherapy of tuberculosis was an impossible goal because of the peculiar properties of the tubercle bacillus and the necrotic nature of tuberculous lesions. Modern chemotherapy can be said to have begun in 1938 with the discovery that sulfanilamide had a limited suppressive effect on the tubercle bacillus, and the introduction of the sulfonamide derivative Promin, which had a definite though limited effect on the course of experimental tuberculosis. In 1944 Waksman (8) and his associates discovered that streptomycin (SM) was highly effective against Myco. tuberculosis in vitro. The experimental studies in animals and the clinical trials which followed this discovery proved that streptomycin was an exceedingly potent agent in vivo and a new era in the treatment of tuberculosis had begun. The fact that tuberculosis was amenable to drug therapy stimulated the study of a great variety of antibiotics and chemical agents which would affect the tubercle bacillus. Most of them never reached the stage of clinical trial, but of those that did, para-aminosalicylic acid (PAS) introduced in 1946 (9) and isoniazid (INH) introduced in 1952 (10), together with streptomycin, have become the standard drugs used in the antimicrobial therapy of tuberculosis. A number of other drugs are useful and will be mentioned later.

Before reporting specifically what these agents will do, it is useful to consider what any drug must accomplish if it is to be effective in tuberculous infection. It must possess certain general qualities to be practical in man, and certain specific qualities which relate to the tubercle bacilli and the special pathology of tuberculosis.

To begin with, the antimicrobial agent should be bactericidal or bacteriostatic in relatively low concentration in blood and

tissue. Since bacterial resistance is the limiting factor of any chemotherapeutic agent, an effective drug is one to which bacterial resistance does not develop or develops very slowly. The "ideal drug" must be freely diffusible and be able to reach all tissues, including the meninges and brain. Since tuberculosis is characterized by tissue destruction and necrosis, the drug must be able to penetrate avascular areas in adequate concentration. It was noted earlier that tubercle bacilli may survive and even multiply within mononuclear cells, so a drug must be able to penetrate cell membrane if it is to affect all the bacilli. Mere availability of the drug is not enough, however, for it must be effective in a variety of biochemical environments. It must be able to act in areas of dense exudate where both living and dead or dying cells are present, and it must be effective within cavities and in dense caseous lesions. It must also be effective against organisms which exist in a variety of metabolic states. If one recalls the pathogenesis of the tuberculous lesion it will be apparent that at different times the metabolic activity of the tubercle bacillus varies widely. Bacilli recently lodged in an area of lung will divide actively until inhibited by mononuclear cells which surround the bacilli. Even then they will continue to be metabolically active as compared with bacilli in caseous lesions where oxygen tension is relatively low. The effective agent should be relatively nontoxic to the host in therapeutic doses, and toxicity must remain low even when the drug is given for prolonged periods. It should be easy to administer, preferably by mouth. Finally, it should be relatively stable and not excreted so rapidly nor altered so quickly by the host that it is impossible to maintain therapeutic levels.

BACTERICIDAL OR BACTERIOSTATIC IN LOW CONCENTRATIONS.—Streptomycin and isoniazid are both potent bacteriostatic agents in low concentration. Streptomycin is effective against most human strains of mycobacterium in concentrations of 0.2–1.0 $\mu$g/ml in vitro using Tween-albumin liquid medium. Isoniazid will inhibit growth in concentrations as low as 0.05 $\mu$g/ml, and PAS produces inhibition at 1.0–2.0 $\mu$g/ml, but inhibition is never complete and is closely related to the size of the inoculum. The problem of whether or not INH or SM are bactericidal or bacteriostatic under certain conditions in vitro is not germane to the present discussion, for neither drug is capable of eradicating infection in vivo. In summary, streptomycin and isoniazid are highly effective in vitro at a concen-

tration easily attained in vivo with moderate dosage. PAS is less effective than either of these drugs.

BACTERIAL RESISTANCE.—In the earliest clinical trials with streptomycin, the development of bacterial resistance was demonstrated, and a tendency to relapse was noted in patients in whom bacterial resistance to streptomycin developed. Following the initial clinical studies by Hinshaw and Feldmann (11), a number of large co-operative studies were begun in this country and in England. The most important of these were the VA-Army-Navy Study begun in 1946 and the British Medical Research Council project begun the same year.

The study by the British MRC was the most carefully

TABLE 1.—STREPTOMYCIN TREATMENT COMPARED WITH UNTREATED CONTROLS*

| | X-RAY IMPROVEMENT, ALL GRADES, % | X-RAY DETERIORATION, % | DEATHS, % | SPUTUM NEG. ON CULTURE, % | SM-RESISTANT BACILLI (AS % OF POS.) |
|---|---|---|---|---|---|
| Controls—bed rest (52 cases) | 33 | 34 | 27 | 4 | |
| SM-treated (55 cases) | 69 | 20 | 7 | 14 | 85 |

*Patients in SM-treated group were given 2 Gm streptomycin daily for four months. These are results two months after stopping therapy. Material taken from British Medical Research Council Report (12).

planned (12). For this study it was decided to treat only patients with acute progressive, bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically positive, unsuitable for collapse therapy and in the age group 15–30 years. Patients were divided into two groups on a random basis, and controls were treated on bed rest while the treated group received 2 Gm SM daily for four months. Table 1 summarizes the results of this study two months after therapy was stopped. That streptomycin had a beneficial effect was unquestioned, but a depressing aspect of the study was the development of bacterial resistance. After four months of treatment 87% of the patients who still had positive sputums were resistant to streptomycin.

It was hoped that the virulence of streptomycin-resistant organisms might be altered, but this was not substantiated in animal experiments and the observation was made repeatedly that clinical deterioration was closely related to the development of resistance. The critical level of resistance was found to be between 10 and 15 $\mu$g/ml, and above this level organisms were totally resistant to treatment. Attempts were made to slow the development of resistance by manipulating dosage and giving the drug for shorter periods of time (six weeks), but these were unsuccessful.

When PAS was introduced and tested clinically, it was found that Myco. tuberculosis developed resistance to this drug too, although more slowly than to streptomycin. After three months of therapy with PAS alone, 24% of cultures still positive were resistant to significant levels of the drug.

Theoretically, tubercle bacilli which invade the host become resistant to a drug in the following manner: As the drug is administered, mutants develop or naturally occurring resistant organisms are present and are not suppressed by the antimicrobial agent. Bacilli sensitive to the drug are inhibited, and gradually the resistant bacilli take over the infection. It is apparent that if another drug *(B)* is administered at the same time as drug *A*, the second drug *(B)* will suppress the multiplication of mutants which are resistant to drug *(A)*. Mutants resistant to both drugs given simultaneously are far less likely to develop than mutants resistant to one drug given alone. This should make it possible, therefore, to preserve bacterial sensitivity for far longer periods than if either drug were given alone.

Combined chemotherapy with streptomycin and PAS had just this effect. It delayed the development of bacterial resistance to both drugs and made possible their administration for much longer periods of time. An MRC study of combined chemotherapy (13) demonstrated that with large doses of PAS the development of streptomycin resistance after three months of therapy was dramatically reduced (Table 2). Other studies demonstrated that mixed populations of varying degrees of resistance may occur in vivo and that the presence of resistant organisms in the sputum is not an absolute contraindication to the continuation of therapy.

When isoniazid was introduced it was rapidly demonstrated that bacterial resistance to this drug also developed. But a

peculiar fact emerged from experimental studies. It was found that some of these resistant organisms had lost their virulence for guinea pigs while retaining it for mice. There was good evidence that isoniazid-resistant organisms were still virulent in man, although the question was raised whether their virulence was not somewhat altered since isoniazid alone seemed to be a remarkably effective drug, certainly more effective than SM alone. It is possible, however, to delay the development of

TABLE 2.—COMPARISON OF PAS ALONE AND IN COMBINATION WITH SM*

| DOSAGE | X-RAY IMPROVEMENT CONSIDERABLE AND MOD., % | SPUTUM CONVERSION ON CULTURE, % | SM RESISTANCE MOD. AND STRONG (AS % OF POS. CULTURES) |
|---|---|---|---|
| PAS alone, 20 Gm/day (59 cases) | 54 | 7 | |
| SM alone, 1 or 2 Gm/day (109 cases) | 71 | 16 | 76 |
| SM 1 Gm and PAS 5 or 10 Gm/day (73 cases) | 88 | 25 | 34 |
| SM 1 Gm and PAS 20 Gm/day | 87 | 23 | 6 |

*Observations of six months after start of treatment. Treatment given for three months. Results of British Medical Research Council (13).

resistance to isoniazid by combined therapy with either PAS or SM, and this is usually the preferred treatment.

DIFFUSION OF DRUG IN VIVO.—All three of the drugs in common use seem to be absorbed readily and blood and tissue levels are adequate. Streptomycin has been demonstrated in cavities in amounts adequate for bacteriostasis. Both INH and PAS have been labeled with $C^{14}$, and tracer studies demonstrate that both drugs penetrate the dense fibrous capsule around chronic tubercles and can be found in adequate amounts even in dense caseous lesions.

PENETRATION OF CELL MEMBRANE.—Working independently,

Suter (14) in this country and Mackaness (15) in England have worked out methods for culturing monocytes which have been infected with tubercle bacilli. The methods are quantitative and allow a measure of the inhibition of growth of bacilli within the cell by various agents. Both have found that isoniazid inhibits the multiplication of intracellular tubercle bacilli in the same concentration as it does in the test tube. In contrast, 20 times as much streptomycin is necessary to inhibit intracellular organisms as is required to inhibit bacilli grown in synthetic media. PAS has no effect on intracellular bacilli.

BIOCHEMICAL ENVIRONMENT OF THE TUBERCLE.—Little is known about this aspect of chemotherapy. Even though a drug may penetrate a dense caseous lesion, the pH of the environment and the presence of a variety of metabolites may alter the effectiveness of the drug. The effectiveness of antimicrobial agents against predominantly exudative disease suggests that exudate per se does not alter their effectiveness.

METABOLIC STATE OF THE TUBERCLE BACILLUS.—A number of investigators have observed that streptomycin and isoniazid have less effect in vitro against resting organisms than against those which are actively multiplying. The biochemical environment and the low oxygen tension of the caseous lesion offers an unfavorable environment for the growth and optimum metabolism of the tubercle bacillus. This very fact may mean that tubercle bacilli which are dormant and yet survive in caseous lesions are less susceptible to drug therapy.

TOXICITY.—In the early trials with streptomycin the usual dosage was 1 Gm daily for three to four months. At this dose level 80% of patients developed toxic symptoms which usually involved the eighth nerve. In a co-operative study by the VA-Army-Navy group it was demonstrated that reduction of dosage to 0.5 Gm daily did not materially reduce the therapeutic effectiveness of the drug but reduced the incidence of toxicity to 7% at the end of three months (16).

The major toxic effect of streptomycin is eighth nerve damage, as evidenced by vestibular dysfunction, and, less frequently, deafness. In 1948, dihydrostreptomycin was introduced with the hope that eighth nerve damage could be reduced, but it was found that this agent produced more deafness, and streptomycin more vestibular damage. Other toxic effects of streptomycin include drug rashes, drug fever, circumoral paresthesias and, rarely, leukopenia and jaundice.

PAS tends to be troublesome because of the gastrointestinal symptoms commonly associated with high doses. Sodium PAS is better tolerated than PAS, but nausea, vomiting, diarrhea and abdominal distention occur often enough to be a handicap. Other reactions to PAS are not common, but hypersensitivity reactions do occur and may even be fatal.

Although a wide variety of toxic effects of isoniazid have been recorded, toxicity has not been a major problem. Most of the toxic effects are related to the central nervous system. Hyperreflexia is common, and peripheral neuritis, toxic psychoses and acute convulsive reactions may occur. Pyridoxine deficiency has been reported with high dosage of INH, and it has been claimed that peripheral neuritis can be prevented by giving pyridoxine (50–450 mg/day). Allergic reactions including chills, fever, dermatitis, arthralgia and purpura have also been recorded, as have hemolytic anemias.

In summary, toxicity is not a major barrier to effective therapy with any of these drugs. The major toxic effect of SM is eighth nerve damage, and patients should be watched carefully during therapy for deafness and vestibular dysfunction. SM should not be used if there is significant kidney damage, since levels become so elevated that eighth nerve damage is likely. INH is relatively safe but should be given with great caution to patients with histories of psychoses or convulsive disorders. PAS is often troublesome because of gastrointestinal upsets, but of greater danger are hypersensitivity reactions. It has been possible to give these drugs for long periods (one to two years) in most patients without major toxic effects.

EASE OF ADMINISTRATION.—Streptomycin must be given by injection, which makes administration outside the hospital difficult. However, it is usually possible to train the patient or a member of the family to administer the drug. Both PAS and INH can be given by mouth. PAS is usually given in a dose of 10–12 Gm daily; the very bulk of medication is a disadvantage, but patients seem to adapt to this readily and this has not been a serious source of trouble. Isoniazid is the easiest drug to administer since the dose is small.

STABILITY.—Streptomycin and isoniazid are relatively stable drugs, but PAS deteriorates on standing and there seems to be some variation in the purity of various preparations of PAS. Little is known about how these drugs may be altered in vivo. Hughes and associates (17) have shown that in certain pa-

tients relatively little unchanged isoniazid may be present in the blood or urine and that patients vary considerably in their capacity to acetylate the compound. Nothing is known about what happens to these drugs in caseous lesions in terms of inactivation. It may be that certain therapy failures are due to inactivation of the drug by the host.

EXCRETION.—Although all of these drugs are excreted fairly rapidly, a good therapeutic effect may be expected with doses below the toxic level.

Chemotherapy falls short of the ideal and infection cannot be eradicated with the drugs now available. It is possible, however, to influence very favorably the balance between host and parasite, and there is little doubt that chemotherapy is now the basis of treatment of all forms of tuberculosis.

## SURGICAL TREATMENT

The common goal of the surgical treatment of tuberculosis is to affect the invading organisms either directly by extirpation of tuberculous lesions or indirectly by collapse therapy. This discussion is concerned chiefly with pulmonary tuberculosis, but the principle of excision of tuberculous disease in other organs is the same. Specific surgical measures are considered later, when tuberculosis of particular organs is reviewed.

COLLAPSE MEASURES.—Although a variety of virtues have been attributed to collapse measures of different types, including pneumothorax, phrenic nerve crush, pneumoperitoneum and thorocoplasty, it is probable that their only significant effect is to close cavities. The effect of cavity closure on the tubercle bacillus is apparent from what has been said about the pathology and bacteriology of the disease. Tubercle bacilli in pulmonary cavities are constantly being expelled into the communicating bronchus and are a constant potential source of superinfection to other parts of the lung, the bronchi, larynx and, if cavities are very large, to the intestine. Bacilli in cavity walls are actively multiplying, since the oxygen supply is usually adequate. In contrast, tubercle bacilli confined to a caseous focus exist in an environment unfavorable for multiplication and become metabolically inactive. Thus any measure which promotes closure of a cavity with production of a caseous focus will indirectly reduce the number of invading bacilli.

PULMONARY RESECTION.—The most definitive type of surgery in pulmonary tuberculosis is resection of the diseased portion of the lung. This may be a segmental resection, a lobectomy or pneumonectomy. Before antimicrobial agents were available the mortality and morbidity of resection made the method impractical. But with modern chemotherapy, pulmonary resection can be done with relative safety in selected cases. Obviously the extirpation of a cavity or cavities directly alters the host–parasite relationship by ridding the host of a major disease focus.

INDICATIONS FOR COLLAPSE OR RESECTION.—In the past collapse measures were used much more frequently than today. Formerly, the fear of massive spread from cavities was constantly present. It was never considered good practice to collapse lung containing fresh exudative disease, but there was always a certain urgency to collapse cavities as soon as possible so that spread could be avoided. This is no longer true. Vigorous antimicrobial therapy makes spread of disease extremely unlikely as long as organisms are drug sensitive. The result is that initial treatment with drugs and bed rest is the rule, and therapy directed specifically at the cavity is delayed until maximum benefit has been derived from these measures. If cavities are relatively recent, they may close with conservative management, and persistence of cavities with negative sputum (on smear and culture) is not uncommon. Some use pneumoperitoneum as a temporary collapse measure early and feel that it hastens recovery. There is no objective evidence for this, however, and in general collapse or resection is reserved for the cavity which remains after an adequate trial of chemotherapy.

The optimum time for collapse or resection is not always easily determined. Ideally it is wise to wait until maximum resolution of the disease process has occurred with chemotherapy and cavities have attained the smallest size that is possible with drugs alone. However, a persistently positive sputum and the presence of a cavity or cavities after six months of adequate therapy is considered an indication for surgical intervention.

The choice of the appropriate procedure in any individual case will be governed by a number of factors, not the least of which is the skill and experience of the surgeon. No absolute criteria can be set down for the particular patient, but certain

general observations can be made concerning the advantages and disadvantages of resection vs. collapse. One of the main concerns of the physician is conservation of pulmonary function and the removal of a diseased segment or several segments produces less diminution of function than surgical collapse. Resection also has the major advantage of getting rid of the cavity completely, and the incidence of successful "sputum conversion" is greater with resection. On the other hand, the incidence of complications is higher with resection than with thoracoplasty or the combination of thoracoplasty and plombage. The resection of residual cavities in the patient with a negative sputum is relatively safe. It is less safe in the patient with persistently positive sputum and becomes much more hazardous if the patient has organisms which are resistant to the antimicrobial agents in common use. The most dreaded complication is bronchopleural fistula following resection; this is the major cause of morbidity and mortality.

Some question might be raised as to the desirability of doing anything surgical about residual cavities in a patient with a persistently negative sputum on smear and culture. There is good evidence that with chemotherapy some cavities are completely healed on pathologic examination even though the cavitary space persists. Complete histologic healing is impossible to predict clinically, however, and the persistence of cavities must be considered a potential danger in the future, particularly after chemotherapy has been stopped.

It should be re-emphasized that the decision to perform a surgical procedure must be highly individualized. Care must be taken to evaluate the patient's pulmonary function carefully before surgery and the risks weighed against the benefits. It may be wise to take considerable risks to salvage a patient with persistently positive sputum, but there is little excuse for making a pulmonary cripple of a patient whose sputum is persistently negative before surgery.

Much has been written in recent years about the wisdom of resecting residual caseous lesions which persist after prolonged chemotherapy. Medlar (18) has emphasized that caseous lesions in the lung are potential cavities and the common source of reactivation of old tuberculosis. Many such lesions have been resected, but it has been discovered that it is very difficult to recover bacilli from the caseous material on culture or animal inoculation. This has raised the question of the wisdom of re-

secting these caseous foci. In a recent pilot study reported by the Veterans Administration the relapse rate in a group which had resection was no smaller than in a similar group which did not have resection done. At present the evidence indicates that resection of residual caseous foci is not essential.

## PRACTICAL CONSIDERATIONS OF DRUG THERAPY

WHO SHOULD BE TREATED.—With the introduction of new drugs and the accumulation of experience in use of these agents in the past decade there has been a gradual change in the attitude concerning what forms of disease should be treated. At first it was believed that only the more acute forms of the disease, such as meningitis, miliary tuberculosis and tuberculous pneumonia, derived much benefit from chemotherapy, but gradually opinion was revised as improvement was noted in the more chronic forms of tuberculosis. Today it is generally agreed that any form of active tuberculosis should receive the benefit of chemotherapy.

WHAT DRUGS SHOULD BE USED.—There is today no ideal regimen of chemotherapy for tuberculosis, and the drugs used will depend to some extent upon the organs infected and the extent of the disease. Enough evidence has accumulated, however, to state that isoniazid is the most valuable drug developed to date and that regimens which include isoniazid are superior to those which use streptomycin as the major drug.

The Committee on Therapy of the American Trudeau Society has suggested the following regimens as acceptable for the treatment of active tuberculosis (19):

1. *Streptomycin-PAS:* 1.0 Gm of streptomycin intramuscularly two or three times weekly and 12 Gm of PAS (or 15 Gm of sodium PAS) daily by mouth in three or four divided doses.
2. *Isoniazid alone:* 5 mg or more of isoniazid per kg of body weight per day in two or three divided doses.
3. *Isoniazid-streptomycin (both daily):* 5 mg or more of isoniazid per kg and 1.0 Gm of streptomycin intramuscularly.
4. *Isoniazid daily-streptomycin twice weekly:* Same dose as in regimen 3, but streptomycin twice weekly instead of daily.
5. *Isoniazid-PAS:* 5 mg or more of isoniazid per kg daily and 12 Gm of PAS daily.
6. *Isoniazid-streptomycin-PAS:* each in dosage as above; streptomycin given daily or twice weekly.

The dosage schedule for tuberculous meningitis and miliary tuberculosis is given later. Which regimen will be used in other forms of tuberculosis, including pulmonary, will depend to some extent upon the prejudice of the clinician. The author feels that the combination of isoniazid and PAS gives excellent results in most cases of pulmonary tuberculosis (not previously treated) and that there is some wisdom in saving a second potent drug (streptomycin) for later use should this be necessary. There does not seem to be any particular advantage in using all three drugs (INH, SM and PAS) except in genitourinary tuberculosis and tuberculous meningitis. Isoniazid alone has been reported to give excellent results in all types of tuberculosis of the skin, and has been used alone successfully in a variety of forms of tuberculosis, since the development of bacterial resistance to isoniazid does not seem to have the same clinical significance as resistance to streptomycin.

How long treatment should be continued.—The co-operative trials by the VA-Army-Navy proved that long-term chemotherapy was superior to treatment for short periods (20). It is now suggested that treatment be continued for at least a year and more often 18 months or even longer. If one considers the pathology and bacteriology of tuberculosis, it is reasonable to assume that long-term therapy should be more effective than short terms of treatment. The outcome of infection is determined by the balance between extension and healing. Chemotherapy with accepted drugs does not eradicate infection but it does tend to tip the balance toward healing and favors the containment of infection. Clinical observations on untreated tuberculosis indicate that the longer the patient remains well after initial diagnosis and treatment, the less likely is relapse. Bacilli contained in caseous areas probably become less and less capable of reactivating infection the longer they remain metabolically inactive. An argument can be made for indefinite prolongation of treatment—or at least treatment might be given during the first two to three years after infection is arrested, since this is the period when relapse is most likely to occur. The solution of this problem will require careful analysis of relapse rates with various regimens, but treatment for indefinite periods already is being tested.

No matter how long treatment is continued, one point seems clear. Chemotherapy of tuberculosis seems to be more effective if therapy is uninterrupted than if intermittent. The choice of

a drug regimen should be made carefully, and the regimen should then not be stopped unless serious toxicity is manifest or unless the bacilli become resistant. There are good theoretic reasons for this principle. Let us suppose that treatment is being given with isoniazid and streptomycin. A few isoniazid-resistant organisms develop but these are still susceptible to streptomycin. As long as therapy is continued, this population of INH-resistant organisms will not multiply. Let us now suppose that therapy is stopped. The INH-resistant organisms may now multiply. If treatment is begun again with INH plus SM there may now be enough INH-resistant organisms so that some of these will become streptomycin-resistant and, as these organisms resistant to both drugs multiply, both drugs become valueless.

OTHER DRUGS USEFUL IN TREATMENT.—A tremendous number of drugs have been screened in vitro for their anti-tuberculous effect, fewer have had some in vivo trial in animals, and a number of these have had clinical trial. A few of these are worthy of mention, for they have certain usefulness in particular cases. Viomycin is approved and available for general use. Toxicity and rapid emergence of resistance make it useful only when neither streptomycin nor isoniazid can be used. Pyrazinamide is not a very potent drug alone but combined with isoniazid seems to be highly effective. A high degree of hepatotoxicity makes its prolonged use impractical. Oxytetracycline has been effectively substituted for PAS for use with streptomycin.

## THERAPY OF SPECIFIC TYPES OF TUBERCULOSIS

Further discussion of the treatment of pulmonary tuberculosis is not necessary here. It should be noted, however, that so-called idiopathic pleurisy with effusion in the patient with a positive tuberculin reaction should be treated as a form of active pulmonary tuberculosis even though bacilli cannot be recovered and no parenchymal lesion can be seen on x-ray. If antimicrobial therapy is not given, between one-third and two-thirds of such patients will develop evidence of active tuberculosis during the next five years.

### MILIARY TUBERCULOSIS AND MENINGITIS

Before the introduction of potent antimicrobial agents for the treatment of tuberculosis, miliary tuberculosis was almost

always fatal and meningitis was uniformly fatal. The fact that any reduction in mortality could be accomplished in these diseases indicates the potency of chemotherapy; and there has been a progressive decrease in mortality since 1945, beginning with the introduction of streptomycin and accelerated by the use of combined therapy and the discovery of isoniazid. In a report of 549 consecutive cases of tuberculous meningitis treated with streptomycin intramuscularly and intrathecally between 1947 and 1950, Lorber (21) gave the two-year survival rate as 31.6% in 1947 and 49.3% in 1948–50. Since the introduction of isoniazid in 1952, others have reported survival rates of 75–90%.

Despite the reduction in mortality, tuberculous meningitis remains a formidable disease and one which requires intensive and often heroic treatment. A number of important factors bear upon the outcome of infection, but by far the most important is the stage of the disease when treatment is initiated. The prognosis is best when the disease is diagnosed in the earliest stage. At this time the symptoms may be quite mild, consisting of moderate headache, malaise, lassitude and afternoon fever. This stage may last for several weeks; and tuberculous meningitis should be considered in the differential diagnosis of any unexplained illness, particularly in a child with a positive tuberculin reaction, and if suspected the spinal fluid should be examined. The next stage of the illness is more characteristic of meningitis and should be diagnosed without much difficulty, for, in addition to an increase in the symptoms already mentioned, there are nuchal rigidity and marked irritability. Photophobia develops and there may be transient shifting paralysis of the extremities. If the disease is untreated there are gradual development of coma and diminished irritability. Coma deepens until death. It is obvious that if one has the good fortune to begin treatment in the first stage of the illness, the results will be far more favorable than if treatment is begun after coma has developed.

Another factor bearing on the outcome of tuberculous meningitis is the presence of significant tuberculous disease elsewhere in the body. In particular, miliary tuberculosis associated with meningitis worsens the prognosis, but significant pulmonary, bone or renal lesions also have an unfavorable effect upon the outcome.

Finally, the patient's age seems to be a factor of some importance. Children below the age of 3 years do not seem to do as well under treatment, although this may be due in part to the stage of the disease when the diagnosis is made. Treatment failures in patients in middle age or older age groups are not as common today, since isoniazid has come into common use, as they were when streptomycin was the only major drug available.

*Early diagnosis* depends upon examination of the spinal fluid, and treatment usually is begun before organisms are found, since it is impractical to wait for cultures or guinea pig inoculation. The characteristic findings are a cell count of 20–2,000/cu mm, lowered sugar and chloride content of the spinal fluid and elevated protein content. Smears should be made and tubercle bacilli sought, but a negative smear should not delay therapy if other findings are suggestive. Cultures should be taken and animal inoculations made before starting therapy.

The *chemotherapy* of tuberculous meningitis and miliary tuberculosis is much more vigorous than that suggested for the other forms of tuberculosis (19). The use of isoniazid is mandatory, and dosage should be 8–10 mg/kg daily for the first 7–10 days, after which it may be reduced to 5–6 mg/kg daily. Streptomycin should also be given in a dosage of 1 Gm daily for the first three months in both children and adults, after which it may be reduced to 1 Gm two or three times a week. Infants may be given 0.5 Gm of streptomycin daily, although children tolerate large doses of streptomycin much better than do adults. PAS should also be given in doses of 12 Gm daily for adults, 8–10 Gm daily for children and 4–6 Gm for infants. Treatment should be continued for at least 18–24 months and possibly longer.

Streptomycin intrathecally has been used extensively in the treatment of tuberculous meningitis and probably was life-saving at times before the introduction of isoniazid. The addition of isoniazid to the therapeutic regimen for meningitis makes the intrathecal use of streptomycin unnecessary, and it is no longer recommended unless the circumstances are exceptional.

One of the most dreaded complications of tuberculous meningitis is the development of basal block. A number of measures have been suggested for the relief of block, but none of them is entirely satisfactory. Purified protein derivative (PPD) intrathecally (22) has been used, chiefly in England, but skull

trephine is a necessary adjunct to this therapy so that prompt decompression by ventricular tap may be done if required after the injection of PPD. The use of the enzymes streptokinase and streptodornase intrathecally has had occasional success. Cisternal tap is useful in children with block, but is not valuable in adults. In spite of these measures basal block remains the most serious complication of meningitis.

Corticotropin and cortisone may have a limited usefulness in the treatment of meningitis, particularly if the development of block is feared. It has been reported that toxic symptoms disappear more rapidly if one of these hormones is used in combination with antimicrobial agents, and they seem to have no deleterious effect in the course of the disease; in fact more rapid clearing of the spinal fluid has been described (7). It seems justified to use either corticotropin or cortisone if toxicity seems overwhelming, or if block is developing. Not enough evidence has accumulated to recommend routine use of these hormones.

Finally, the patient with tuberculous meningitis often presents a formidable nursing problem. Nasal feeding may be necessary in the early months of treatment, and good nursing may mean the difference between success and failure.

## Tuberculosis of Bone

The introduction of antimicrobial agents for the treatment of tuberculosis (streptomycin in particular) has reduced the mortality and morbidity from tuberculosis of bone, but the very nature of the disease has kept it a surgical problem. Tuberculosis of bone and joint is not usually diagnosed until the disease has been present many months and there has been sufficient destruction of bone or encroachment upon the joint space to be recognizable by x-ray. Often soft tissue abscesses and sinus tracts complicate the disease, and it is not surprising that chemotherapy alone is inadequate for cure. Tuberculosis of the spine and hip are likely to be moderately advanced before a diagnosis is made, but tuberculosis of the knee may be diagnosed early enough to induce healing without surgical intervention.

Bone and joint tuberculosis almost always represents a hematogenous spread of the disease, and usually a spread from primary infection. It is common, however, for active dis-

ease in bone to become manifest months or even years after the primary infection. Less commonly, tuberculosis of the spine is thought to result from direct extension from contiguous caseous lymph nodes. Tuberculosis of the lung, kidney or other organs should be suspected and searched for in every case of tuberculosis of bone. The most frequent site of skeletal tuberculosis is the spine, with the hip and knee next most common, and other joints, including ankle, shoulders, elbow and wrist, less common.

Some idea of the seriousness of skeletal tuberculosis is given by the figures cited by Martensen (23) in a review of 418 cases of tuberculosis of the spine in children diagnosed in one district in Sweden between 1900 and 1949. Of this group, 45.3% died directly or indirectly of tuberculosis. The death rate gradually decreased during the period under study, and certainly the death rate has declined sharply with the introduction of chemotherapy.

*Chemotherapy.*—Unfortunately there are no very adequate studies of different regimens of treatment for skeletal tuberculosis. The type of clinical study of pulmonary tuberculosis carried out so well by the VA-Army-Navy group and the British MRC are conspicuously lacking when it comes to a study of skeletal tuberculosis. Streptomycin has become the drug of choice for the orthopedic surgeon, but it is given in a variety of ways with or without PAS and for varying lengths of time. Little information is available concerning the efficacy of isoniazid, and evidence has been presented (without controlled comparison) that it is not as effective as streptomycin when given alone (24).

At present, streptomycin combined with PAS is the regimen most used by orthopedic surgeons. Whether or not isoniazid combined with streptomycin or PAS will be as good or better remains to be seen, but judging from the results of treatment of other types of tuberculosis it should be effective. Long-term therapy should be used and it should be uninterrupted.

*Other measures of treatment.*—Conservative measures of treatment of skeletal tuberculosis continue to be used with good effect, including immobilization of joints, rest, spinal fusion and arthrodesis. Chemotherapy has made possible more radical surgical procedures than were formerly possible. Not only can deep-seated abscesses be removed with tight closure of incisions, but curettage of vertebral bodies has been successfully

accomplished without later evidence of spread of infection.

Much needs to be done to evaluate present-day therapy of skeletal tuberculosis, and only long-term follow-up will give the answers to many pressing problems of therapy.

## Genitourinary Tuberculosis

Tuberculosis of the genitourinary tract is a form of hematogenous disease and should be suspected and looked for in every case of pulmonary tuberculosis, skeletal tuberculosis or miliary disease. The incidence of tuberculosis of the kidney to some extent reflects the care with which it is sought. A few pus cells in the urine may be the only manifestation of the disease and pyelograms may be entirely normal. Diagnosis in such cases must be made by finding tubercle bacilli on culture or guinea pig inoculation of concentrates of 24 hour urine collections. At least three such 24 hour specimens should be collected. Cystoscopy and collection of urine from each ureter for culture and animal inoculation is also a useful diagnostic aid. If tuberculosis is found anywhere in the male genital tract, including epididymis, prostate or seminal vesicle, renal tuberculosis should be suspected.

According to Lattimer (25), the regimen of choice in treatment of genitourinary tuberculosis is 1 Gm of SM twice weekly, 5 mg of INH per kg daily and 12 Gm of PAS daily, continued for at least a year and probably longer. All of the combined drug regimens have merit, however, and it may be that PAS and INH will prove to be as effective as all three drugs. If tuberculosis of the kidney is found on bacteriologic study but no destruction is evident on pyelography, complete resolution of the disease may be anticipated without surgical intervention.

The presence of one destroyed kidney or a cavity in one kidney is still an indication for surgical intervention, but it should be remembered that chemotherapy for one to four months is advisable before surgery is performed. Nothing is to be gained by operating too early, as there is always danger of spread. If the kidney is destroyed or contains several cavities a nephrectomy is necessary, but if only one pole of the kidney is involved a segmental resection of the involved area will accomplish the removal of the infected area while preserving kidney function. Chemotherapy should be continued for at least eight months

after surgery. If bilateral renal disease is present, with destruction of portions of both kidneys, nothing is gained by surgical intervention, and such cases should be managed medically with prolonged chemotherapy. It may be advisable to continue drug treatment indefinitely unless toxic symptoms develop.

In general, tuberculous epididymitis responds well to chemotherapy, and surgical excision is necessary only if enlargement of the caseous area continues or a sinus tract develops. Tuberculosis of the prostate, seminal vesicles and bladder also responds well to chemotherapy. Late scarring and contraction of the urinary bladder may necessitate cutaneous ureterostomy to avoid back-pressure on the kidneys.

## Other Forms of Tuberculosis

Childhood tuberculosis.—Until the introduction of INH there was some question as to whether or not chemotherapy had any significant effect on primary infection. Lincoln (26) believed that SM and PAS did not seem to alter significantly the incidence of serious complications, such as miliary tuberculosis and meningitis. There is uniform agreement, however, that INH does prevent these complications, and only one case of tuberculous meningitis has ever been reported as developing during isoniazid therapy, and this was in an adult. It is not uncommon for meningitis to occur while patients are receiving PAS and SM.

The treatment of choice is INH and PAS, continued at least a year. Any patient with evidence of an active primary infection should receive therapy. The only question is the treatment of the recent tuberculin converter. Should such a patient be treated if the only evidence of infection is the conversion of the tuberculin reaction from negative to positive? There are differences of opinion on this point, but many agree that children less than 3 years of age who convert should receive chemotherapy, since the incidence of serious hematogenous spread is higher in the early age group.

Pelvic tuberculosis.—Tuberculosis of the female genitalia is relatively uncommon and the diagnosis very difficult to make on the basis of history and pelvic examination. The commonest symptom is dull lower abdominal pain; other complaints are backache, leukorrhea, dysmenorrhea and menstrual irregularities. Patients in the age group 16–25 usually present with

symptoms of pelvic disease. Between 25 and 40 years, infertility is the commonest complaint and often the only symptom, whereas after age 40 the disease is likely to be found at laparotomy or after curettage (27). Signs and symptoms of peritonitis are frequent, and tuberculosis of the pelvis may be found during search for the cause of ascites.

Pelvic tuberculosis is usually considered to be the result of hematogenous spread at the time of primary infection, and in about 80% of cases there is evidence of a primary infection elsewhere. It is of interest that female genital tuberculosis rarely is found in children and seems to be a complication of primary infection which occurs in adolescence or early adult life. Since today primary infections are likely to occur later in life, it may be that pelvic tuberculosis will become relatively more common in terms of the incidence of tuberculous infection. The high incidence of tuberculous peritonitis in patients with pelvic tuberculosis has led some authorities to conclude that pelvic tuberculosis is secondary to spread from the peritoneum, but it is more likely that spread occurs in the opposite direction. The fallopian tubes are most commonly involved, the endometrium next in frequency, involvement of the ovaries occurring in about 20% of cases, while tuberculosis of the cervix and vagina is quite rare. Since sterility is a common presenting complaint, it is not surprising that pregnancy is rare in the presence of pelvic tuberculosis. It may occur, however; and if it continues to term there is danger of congenital tuberculosis.

The findings on pelvic examination are nonspecific, and the diagnosis rests on histologic demonstration of tuberculous tissue and specific bacteriologic evidence. Tissue obtained by curettage should be cultured and used for animal inoculation. At times, bacteriologic examination of menstrual blood is used in diagnosis. If pelvic tuberculosis is demonstrated, careful search should be made for tuberculosis elsewhere in the body, particularly in lung and pleura.

Chemotherapy should be instituted in every case of diagnosed pelvic tuberculosis. Any of the accepted regimens of therapy may be used. Rest and sanatorium care depend on the extent of the disease and presence of extragenital tuberculosis.

Surgery is not an emergency procedure, and the disease should be treated medically for the first five to six months. If pelvic masses persist at the end of this time, surgical excision should be done, but chemotherapy should be continued for six

to eight months after surgery. Not enough experience has accumulated to know how much improvement can be expected from long-term chemotherapy, but it is likely that much less excisional surgery will be necessary in the future.

TUBERCULOUS LYMPHADENITIS.—Too often tuberculosis of lymph nodes is considered a localized process which can be treated locally. Careful search for other tuberculous foci usually reveals tuberculosis elsewhere in the body, particularly in lung, so it should always be considered a part of a systemic disease. Not infrequently tuberculosis is diagnosed at the time of biopsy of an enlarged lymph node thought to be the manifestation of some other disease, particularly lymphoma. Adenitis is no longer a disease of childhood and is frequently seen in adults, even in older age groups.

There is no uniformity of opinion concerning treatment of this form of tuberculosis, and no very good studies have been reported. It is known that nodes diminish in size slowly with chemotherapy, and if drugs are given for short periods (two to three months) exacerbation of the infection is common. Both surgical excision and roentgen irradiation have been reported to be effective, but no follow-up studies are reported concerning relapse rates.

At present the following approach to the problem seems reasonable. Tuberculosis of the lymph nodes should be considered a part of a systemic disease and foci of infection elsewhere should be sought. Long-term therapy on any of the accepted regimens should be given. If response to chemotherapy is slow and large abscesses persist, surgical excision should be done. X-ray therapy seems to have little to offer.

TUBERCULOSIS OF THE INTESTINE AND LARYNX responds well to chemotherapy. Usually these conditions are associated with far-advanced cavitary disease of the lung, and if the pulmonary disease can be controlled disease of the intestine or larynx will improve.

## SUMMARY

1. Tuberculosis is a chronic relapsing disease caused by the tubercle bacillus and characterized by tissue destruction.

2. The outcome of infection depends on the balance between the resistance of the host (both natural and acquired) and the number and virulence of the invading bacilli.

3. Treatment is directed toward enhancing host resistance and reducing the number of invading organisms.

4. Host resistance may be enhanced by bed rest and sanatorium care, as well as good nutrition.

5. Chemotherapy does not eradicate infection, but promotes healing by reducing the number of invading organisms. The major drugs in use today are streptomycin, isoniazid and para-aminosalicylic acid. The use of several drugs at the same time reduces the rate of development of bacterial resistance and makes possible long-term therapy.

6. Surgery for tuberculosis is directed toward reducing the bacterial population either by excision of diseased areas or by collapse of cavities, thus rendering the environment of the bacilli less favorable for growth.

7. All active tuberculosis should receive the benefits of chemotherapy and, in general, treatment should be continued for at least a year.

8. The treatment of specific forms of tuberculosis is discussed.

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